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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,682	01/06/2006	Mark T. Gladwin	4239-67618-05	3411

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EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,682	GLADWIN ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *16-19,24-28 and 33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,20-23,29-32 and 39-41* is/are rejected.

7)☒ Claim(s) *33-38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/2/09 has been entered.

The restriction requirement and Applicant's election filed on 1/28/08 remains in force.

Claim 41 is new. Claims 1-41 are pending. Claims 16-19 and 24-28 have been withdrawn as being directed to non-elected subject matter. Claims 33-38 are withdrawn from consideration because they are dependent upon withdrawn claims. Therefore, claims 1-15, 20-23, 29-32, 39, 40, and 41 are under examination as they read on the elected subject matter.

Withdrawn rejections:

Applicant's amendments and arguments filed 7/2/09 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claim 1-4, 9, 11, 12, 20, 29-32 and 40 were rejected under 35 U.S.C. 102(b) as being anticipated by Zapol (WO 94/00180). Applicant has amended the claims and the Examiner withdraws the rejection. Claims 1-15, 20-23, 29-32, 39 and 40 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al.

(Abstract: J. Cereb. Blood Flow Metab. 1994, 14(2), 217-26) in view of Modin et al. (Acta Physiol Scand 2001, 171, 9-16 and, with respect to claims 13-15, Nachtsheim (West J Med. 1998, 169(2), 112-113). This rejection is withdrawn in favor of the rejections to follow.

Claim Objections

Claims 33-38 are objected to because of the following informalities: claim 16 has been withdrawn from consideration and all claims dependent on claim 16 should also be withdrawn. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7-9, 11-13, 20-23, and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Shaw et al. (US 4650484).

Shaw et al. disclose methods for treating **ischemic conditions** in a patient (which inherently reads on a human) having such a condition by administration of a therapeutically effective amount of a vasodilator internally and transdermally to treat the condition (Abstract and claims 1-13). Shaw et al. teach **buccal** administration to get the vasodilator into the systemic circulation which means that it contacts the blood (claim 7).

It is inherent that the nitrite reacts in the presence of hemoglobin in the subject to release nitric oxide. **Sodium nitrite**, which is not acidified, is specifically named as a vasodilator in a finite list of vasodilators (column 2, lines 35-45). Thus, instant claims 1, 2, 7-9, 11 and 12 are anticipated. Since the same effective amount of nitrite is disclosed by Shaw et al. as instantly claimed then the method inherently induces production of no more than about 25%, 20%, 10%, 8%, 5% or 3% methemoglobin and anticipates instant claims 3, 4, and 29-32. The method is to increase the supply of oxygen to the tissue such as the heart, which would be an ischemic heart (ischemic cardiac tissue and hence a cardiovascular condition) and thus anticipates instant claims 20-23 (column 2, lines 51-68). The vasodilator is administered with another agent, which is another vasodilator (claim 1) and reads on instant claim 13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-15, 20-23, 29-32, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (US 4650484) and Modin et al. (Acta Physiol Scand 2001, 171, 9-16 and, with respect to claims 13-15, Nachtsheim (West J Med. 1998, 169(2), 112-113) and Matthew (Quarterly Journal of Medicine, 1908 (2), pp 261-278) and Goldfrank et al. (Goldfrank's Toxicological Emergencies 7th Edition 2002, page 1511).

Applicant claims a method for treating a subject having a cardiovascular condition comprising administering to the subject an effective amount of a non-acidified pharmaceutically-acceptable salt of nitrite for a sufficient period of time to induce vasodilation and/or increase blood flow in the subject thereby treating the subject, wherein the administration is by a route whereby the pharmaceutically acceptable salt of nitite contacts blood in the subject, and the route is selected from the group consisting of intravenous injection, intramuscular injection, buccal, rectal, ex vivo, intraperitoneal, intravenous, intraarterial, subcutaneous, inhalation, intramuscular, and into a cardiopulmonary bypass circuit.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The reference of Shaw et al. is decribed in detail above and that discussion is herby incorporated by reference. *Shaw et al. establish the concept of treating ischemic conditions with non-acidified sodium nitrite.*

Matthew and Goldfrank et al., establish that non-acidified sodium nitrite is well known in the art of vasodilators to be a vasodilator. Matthew described in 1908 that a decrease in blood pressure was observed due to administration of 2 grains of sodium nitrite in water to a subject (page 263, Nitrites and Nitrates employed; Figure 4, page 267 and accompanying text). Goldfrank et al. clearly teach that administration of nitrite, such as sodium nitrite, induces vasodilation and enhances organ blood flow via denitration with subsequent release of nitric oxide (page 1511, left column). Intravenous injection of sodium nitrite results in oxidation of hemoglobin on a mole-per-mole basis (page 1511, right column). Goldfrank et al. suggest a bedside hemoglobin measurement to guide the nitrite therapy to avoid excessive methemoglobin formation (page 1511, lower right column). ***Therefore, the conventional wisdom for one of ordinary skill in the art of vasodilation is that non-acidified sodium nitrite is a vasodilator.***

Modin et al. teach that nitric oxide is derived from nitrite (title) and that physiologically relevant concentrations of nitrite evoke vasodilation (page 13, right column Discussion; and page 15, left column last paragraph). Modin et al. teach that the relaxatory effect of nitrite was increased at pH 6.6 over neutral pH (Abstract). Thus Modin et al. teach that **non-acidified nitrite** also has relaxatory effects similar to "acidified" nitrite (see figures 1, 2, figure 5 and respective discussion in the text). Modin et al. administered various amounts of **sodium nitrite** but noted a threshold response of

10 microM and near relaxation to basal tone at 1000 microM for the non-acidified sodium nitrite (page 11, Results). Modin et al. teach adding additional agents (ascorbic acid) to enhance the effect of the sodium nitrite (Abstract) Modin et al. conclude that inorganic nitrite evokes vasodilation most likely through nitric oxide release and that this effect is increased if the pH of the environment is reduced to levels normally found in tissues during **ischemia**/hypoxia (page 15, last paragraph).

Nachtsheim teaches that **sildenafil** is a known promoter of vasodilation that can enhance sexual experience (see whole article). Nachtsheim teaches that sildenafil works in conjunction with nitric oxide to enhance the vasodilatory effect. Nitric oxide signals cGMP production which then causes smooth muscle relaxation. Sildenafil blocks the enzyme responsible for degradation of cGMP thus leading to higher sustained levels of cGMP and relaxation of the smooth muscle (Page 112).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Shaw et al. is that Shaw et al. do not expressly teach of 0.6 to 240 microM of sodium nitrite or injection of about 36 micromoles per minute for at least 5 minutes into the forearm brachial artery of the subject or a circulating concentration in blood of the subject of no more than 20 microM. This deficiency in Shaw et al. is cured by the teachings of Modin et al. and Goldfrank et al.

2. The difference between the instant application and Shaw et al. is that Shaw et al. do not expressly teach addition of sildenafil in the method. This deficiency in Shaw et al. is cured by the teachings of Nachtsheim.

3. The difference between the instant application and Shaw et al. is that Shaw et al. do not expressly teach injection or inhalation for the route of administration. This deficiency in Shaw et al. is cured by the teachings of Goldfrank et al. and common sense.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sodium nitrite within the range instantly claimed and injection of about 36 micromoles per minute for at least 5 minutes into the forearm brachial artery of the subject or a circulating concentration in blood of the subject of no more than 20 microM, as suggested by Modin et al. and Goldfrank et al., in the method of Shaw et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Shaw et al. teach *a therapeutically effective amount* to the systemic circulation to treat an ischemic condition in a patient and Modin et al. suggest how much sodium nitrite would be beneficial for use in tissues during ischemia. Modin et al. also indicate that human plasma has 0.45 microM nitrite and human serum has 6.6 microM nitrite (page 14, left column) so it is obvious to administer an amount of nitrite that would increase

the plasma and serum concentration above the basal level for a therapeutic effect. It is merely routine optimization to obtain a circulating concentration of not more than 20 microM.

In another line of argument, since Shaw et al. teach a therapeutically effective amount then it is merely routine optimization to arrive at the instantly claimed amounts and measurement of the circulating concentration in the absence of evidence to the contrary. The amount of a specific ingredient in a composition is clearly a result effective parameters that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention.

In addition, it is merely judicious selection of injection into the brachial artery and routine optimization the instantly claimed amount of sodium nitrite for that the instantly claimed time period by one of ordinary skill in the art of medicine in the absence of evidence to the contrary. The expected result remains increasing the systemic circulation of nitrite. Furthermore, the broad claims of Shaw et al. include all ischemic tissue types which would be known to one of ordinary skill in the art of medicine.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use sildenafil, as suggested by Nachtsheim, in the method of Shaw et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is established that sildenafil, a promoter of vasodilator, enhances the action of nitric oxide thus presenting an improved treatment protocol for the patient with the added benefit of potential enhanced sexual activity for the patient. Furthermore, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

3. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use inhalation or injection as the route of administration, as suggested by common sense and Goldfrank et al., in the method of Shaw et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Shaw et al. is directed to getting the vasodilator into the systemic circulation. Goldfrank et al. teach intravenous administration which provides the vasodilator to the systemic circulation. Other forms of administration such as parental, rectal, ex vivo, peritoneal, intraarterial, subcutaneous, inhaled, intramuscular or cardiopulmonary bypass circuit modes of administration are obvious to one of ordinary skill in the art of medicine

especially when Shaw et al. is directed to getting the vasodilator into the systemic circulation.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976).

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments:

Applicant's arguments are moot in view of the new ground of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 6-13, 20-23, 39, 40 and 41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, and 9-15 of copending Application No. 10/563,683. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the instant invention embraces or is embraced by the subject matter of the copending application. One of ordinary skill in the art would recognize the methods in the copending application of treating brain ischemia—reperfusion (medical conditions associated with the cardiovascular system) by decreasing blood pressure and or increasing vasodilation with a non-acidified sodium nitrite to a subject. The same concentrations of sodium nitrite (0.6 to 240 micromolar) are claimed as well as the subjects and routes of administration (intravenous and inhalation). The same amount administered would result in the same circulating concentration.

The copending application does not expressly teach treating a subject having a medical condition associated with the cardiovascular system.

However, one of ordinary skill in the art would have recognized cardiac ischemia reperfusion and cerebral artery vasospasm as medical conditions associated with the cardiovascular system.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to arguments:

Applicant requests that the rejection be held in abeyance until allowance. Until that time, the rejection is maintained.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bryson (Comprehensive Review in Toxicology for Emergency Clinicians 1996, 3rd Edition, page 361) also establishes intravenous sodium nitrite as a vasodilator.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1616